REMARKS/ARGUMENTS

Claim 16 has been revised to more explicitly note the known relationship between the P23H mutant opsin genotype and retinitis pigmentosa as an autosomal dominant condition. Support for this recitation of a known relationship is found at least on page 2, lines 14-16, of the application as filed (or paragraph [0007] in the US 2004/0242704 published version of the application).

Claim 16 has also been revised to feature a derivative of a 9-cis retinal wherein the derivative has a modified polyene chain with retention of the polyene chain length and retention of the 9-cis bond. Support for a modified polyene chain is found at least in paragraph [0037] of US 2004/0242704 (the published version of the instant application). That paragraph clearly discloses that a retinoid of the invention may be "a derivative of an 11-cis-retinal or 9-cis-retinal that has a modified polyene chain."

Support for the retention of the polyene chain length is found at least in previous Claim 47 as well as paragraph [0031] of US 2004/0242704, which discloses that a retinoid of the invention may optionally have a "modified polyene chain length". This paragraph discloses the alternative elements of a polyene chain with and without a change the chain length, and so either one may be excluded via the language of the claims. See *In re Johnson* 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining.").

The revisions to Claim 16 are made to better tailor the claims to currently contemplated commercial embodiments of the invention and so are made for reasons related to business considerations rather than any issue of record. Applicants expressly reserve the right to re-present any previously pending version of Claim 16 without prejudice in a continuing application. Similarly, Applicants expressly reserve the right to re-present canceled Claims 21, 38-43, 45, 47, and 48 in a continuing application without prejudice.

Claims 17 and 18 have been revised to correct a clerical oversight in the use of "a vertebrate." Claims 17, 18, and 35-37 have been revised to correspond to the changes in Claim 1.

Claim 19 has been revised to feature a specific structure supported at least by disclosed formula XIII on pages 11-12 of the instant application as filed. Claim 20 has been revised to feature a specific structure within that formula.

New Claims 49 and 50 have been introduced to explicitly note the known production of rhodopsin within a human subject with P23H mutant opsin, indicating the availability of endogenous 11-cis-retinal. Support for these claims is found at least on page 5, lines 1-10 and 22-24, of the application as filed (or paragraphs [0005] and [0008] in the US 2004/0242704 published version of the application). New Claim 51 has been introduced to present the feature of determining the presence of the mutant opsin before the act of administering. Support is provided at least on page 6, lines 18-30; and page 17, lines 15-16 (or paragraphs [0025] and [0066] in the US 2004/0242704 published version of the application).

No new matter has been introduced, and entry of the revised claims is respectfully requested.

Initial Matter/Citation of Cited Document

Applicants wish to point out the following point before addressing the Office Action mailed January 27, 2009 in detail.

The citations of Berson ("Retinitis pigmentosa: Unfolding its mystery") on pages 5 and 7-8 of the Action were not accompanied by any bibliographic information and without any copy being provided to Applicants. Therefore, Applicants have provided a form SB/08 herewith with citation of the Berson document. The initialing of the form, which also cites other documents discussed herein, is respectfully requested.

Restriction Requirement/Elected Invention

The Action mailed January 27, 2009 asserts that Claims 47 and 48 "are not directed to the elected species of 11-cis-7-ring retinal and are withdrawn from consideration as being directed to a non-elected invention."

Applicants have carefully reviewed both claims and respectfully point out that Claim 47, like Claim 16 from which it depends, is generic to the elected species and so necessarily encompasses the species. More specifically, Claim 47 further defines the opsin-binding synthetic retinoid of Claim 16 as "a derivative of 11-cis-retinal or 9-cis-retinal, wherein said derivative comprises *the 20 carbon backbone of said 11-cis-retinal* or 9-cis-retinal" (italics added).

The structure of the elected species of 11-cis-7-ring retinal is shown in Figure 1b of the instant application. That illustration makes it clear that the 20 carbon backbone of the 11-cis-retinal is present. Applicants respectfully point out that the presence of carbon and hydrogen atoms in the "7-ring" does not alter the physical and structural presence of the 20 carbon backbone in Claim 47.

Accordingly, Applicants respectfully submit that the withdrawal of Claim 47 from consideration was in error and that Claim 47 should have been searched and examined with the other claims.

Applicants further point out that the above-revised claims are directed to a scope that is highly similar to that of Claim 47. And with the filing of the accompanying Request for Continued Examination (RCE), the revised claims may be searched and examined without undue burden.

Furthermore, and given the RCE, Applicants respectfully request a shift of the elected species from be changed from 11-cis-7-ring retinal (elected via the response filed February 8, 2008) to the compound encompassed by Claim 20. The structure of that compound is clear from Claim 20, and Applicants respectfully point out that the compound is a methyl ketone at position C15. All of the pending claims read on this elected species.

And with respect to the Requirement for Election of Species between oral and local administration set forth in the Office Communication mailed December 10, 2007, Applicants elect oral administration. Applicants point out their understanding that an Election of Species requirement is used to facilitate the necessary search and that should an elected species be found allowable, search and examination continues with the next species. Confirmation of this understanding in the next Office Communication is respectfully requested.

Alleged Rejections Under 35 U.S.C. § 112, first paragraph

Claims 16-21, 35-43, and 45 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not supported by an adequate written description. Applicants have carefully reviewed the statement of the rejection and respectfully traverse because no *prima facie* case of an inadequate written description is present.

Despite Applicants' careful review of the instant rejection, the exact basis of the rejection is unclear. The statements regarding an example of administration to a human subject (on page 3 of the Action) and cell line tests appear to be an improper requirement for actual reduction to practice where no such requirement exists in U.S. patent law.

And the comment regarding "any condition other than retinitis pigmentosa expressing a mutant opsin protein with a substitution of Proline 23 with Histidine" (on page 3 of the Action) appears to allege the possibility, without any evidence, of the substitution (mutation) causing a condition other than retinitis pigmentosa. So the instant rejection appears to be based, at least in part, on an unsubstantiated allegation.

In light of the above, no *prima facie* case of an inadequate written description is present, and this rejection may be properly withdrawn.

Claims 16-21, 35-43, and 45 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled for the full scope of the claims. Applicants have carefully reviewed the

statement of the rejection and respectfully traverse because no *prima facie* case of non-enablement is present.

As an initial matter, Applicants point out the well established standard that an application must be taken as presumptively enabling unless there is objective reason to doubt the statements contained therein (see MPEP 2164.04 and the case decisions cited therein, such as *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)). This presumption places the burden of the *prima facie* case on the Office.

But Applicants' careful review of the instant rejection shows that the requirement for objective reasoning and evidence has not been met. As a result, Applicants believe that clarification of the record is necessary.

On page 5, numbered paragraphs (3) and (4) of the Action only rely on two cited documents. But the citation of Berson ("Retinitis pigmentosa: Unfolding its mystery" Proc. Natl Acad Sci, USA, 93:4526-4528, 1996) is not relevant to the pending claims because vitamin A is not a 9-cis-retinal derivative as featured in the claims. Therefore, the cited document is not relevant to the instant claims.

Additionally, the alleged "mystery of different forms of retinitis pigmentosa" reported by Berson is not relevant because the claims are not directed to "different forms of retinitis pigmentosa." To the contrary, the claims feature a specific form of retinitis pigmentosa due to a specific mutation of opsin.

Similarly, the citation of Chatzinoff et al. (USP 3,196,078) is also not relevant because the 11-cis-isomer of vitamin A is not a 9-cis-retinal as featured in the claims.

(As for the assertions of these documents against the previously pending claims, Applicants respectfully point out that none of the documents are relevant to an *opsin-binding synthetic retinoid* as previously featured in the claims.)

In light of the above, there is simply no adequate analysis of the "state of the prior art" or the "predictability or unpredictability of the art" as set forth by the title for numbered paragraphs (3) and (4).

As for the allegations on page 5, numbered paragraphs (6) and (7) of the Action, the statements regarding Applicants' disclosure concerning 11-cis-7 ring retinoids, 11-cis-6-ring retinal, and 11-cis-9-demethyl-7-ring retinal were improperly asserted against Applicants, especially given the failure to recognize that Figure 2D provides guidance regarding the successful use of 11-cis-7-ring retinal and 11-cis-retinal to regenerate P23H-rhodopsin. Nevertheless, the allegations are not relevant to the pending claims as revised above.

The instant rejection provides no objective reasoning as to why a 9-cis-retinal derivative of the pending claims would not be expected to work in the practice of the claimed methods. And to the extent that the instant rejection is based on an allegation that these retinal derivatives are not part of working examples of the invention, Applicants point out that actual reduction to practice is not required in U.S. patent law to prevent the presence of undue experimentation.

In light of the above, the conclusion of excessive and undue experimentation on page 6 of the Action is not adequately supported.

Instead, Applicants point out that the absence of undue experimentation is not equivalent to the necessary presence of absolute predictability and/or the lack of experimentation. To the contrary, a need for routine and repetitive experimentation is wholly consistent with the presence of an enabling disclosure (see the facts of *In re Wands* as cited in the instant rejection). As stated in the rejection, "enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation to make or use the invention."

Because no more than routine and repetitive experimentation is necessary to make and use the claimed methods, the instant rejection is misplaced and may be properly withdrawn.

Alleged Rejections Under 35 U.S.C. § 112, second paragraph

Claims 16-21, 35-43, and 45 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

The first rejection under this statute alleges that the claims are unclear "as to what conditions have a loss of photoreceptor function from the expression of a mutant opsin protein with a substitution of Proline 23 with Histidine." Applicants respectfully submit that this is not a relevant issue because the claims as rejected would be simply understood by the skilled person as featuring the treatment of a human subject with that substitution mutation in opsin. This is readily understood and can be determined by known genotype analysis as a non-limiting example. There is simply no need for the skilled person to know what possible "conditions" may result from this mutation because that is not a feature necessary to the claims. Accordingly, the metes and bounds of the claims are clear and this rejection may be properly withdrawn.

Claims 17, 18, 39, and 40 were rejected due to use of the term "vertebrate," which is not found in Claim 16. Applicants have corrected this oversight in the revised claims, and so this rejection may be properly withdrawn.

Alleged Rejections Under 35 U.S.C. § 102

Claims 16 and 17 were rejected under 35 U.S.C. § 102 as allegedly anticipated by Kupfer et al. (1993) or alternatively Berson (as cited above). Applicants have carefully reviewed the statement of the rejection as well as the cited documents and respectfully point out that neither document teaches or suggests the use of a 9-cis-retinal derivative as featured in the claims. Accordingly, this rejection may be properly withdrawn.

Alleged Rejections Under 35 U.S.C. § 103

Claims 16-18 and 45 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Chatzinoff et al. (USP 3,196,078). Applicants have carefully reviewed the statement of the rejection as well as the cited document and respectfully point out that the document fails to teach or suggest the use of a 9-cis-retinal derivative as featured in the claims. Accordingly, this rejection may be properly withdrawn.

Claims 16-21, 35-43 and 45 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Chatzinoff et al. (USP 3,196,078) in view of Kuksa et al. (2002) and Klimko (USP 6,300,328). Applicants have carefully reviewed the statement of the rejection as well as the cited documents and respectfully point out that none of the documents, whether each is taken alone or in any combination with another, teaches or suggests the use of a 9-cis-retinal derivative as featured in the claims. Accordingly, this rejection may be properly withdrawn.

Alleged Double Patenting

Claims 16-22, 35-43, and 45 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 8-11, 59, 62, and 70-104 of copending application no. 10/548,612. Applicants have carefully reviewed the statement of the rejection and respectfully traverse because no case of obviousness-type patenting is present.

This rejection alleges that the claims of the instant application *may* overlap in scope with the claims of the copending application. This rejection asserts that "it is unclear what other conditions are addressed with the mutant opsin P23H ... such as LCA...."

But as Applicants explained above with respect to the allegation of an inadequate written description, there is no evidence that the substitution (mutation) is capable of resulting in LCA or any other condition featured in the claims of the copending application. So the instant rejection appears to be based on an unsubstantiated speculation of what *may* be an overlap. Applicants respectfully submit that such speculation is not an adequate basis to support a *prima facie* case of nonstatutory obviousness-type double patenting.

Moreover, and in light of the provisional status of the instant rejection, no action is believed necessary until the claims in at least one of the two applications are held to be allowable. So in the event that this rejection is maintained despite the above, Applicants respectfully request that this rejection be held in abeyance until such time as the claims in at least one of the two applications are allowed.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at number below.

Respectfully submitted,

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